the behavioral consequences of lack of CD38, it seems likely that CD38-mediated mechanisms are also involved in the release of oxytocin (and possibly other neuropeptides) within the brain. The results make a search for human *CD38* mutations tempting, for example in patients with severe disturbances in social behaviors, including social phobia and autism.

REFERENCES

Dluzen, D.E., Muraoka, S., Engelmann, M., Ebner, K., and Landgraf, R. (2000). Eur. J. Neurosci. *12*, 760–766.

Empson, R.M., and Galione, A. (1997). J. Biol. Chem. *272*, 20967–20970.

Ferguson, J.N., Young, L.J., Hearn, E.F., Matzuk, M.M., Insel, T.R., and Winslow, J.T. (2000). Nat. Genet. *25*, 284–288.

Jin, D., Liu, H.X., Hirai, H., Torashima, T., Nagai, T., Lopatina, O., Shnayder, N.A., Yamada, K., Noda, M., Seike, T., et al. (2007). Nature *446*, 41–45.

Landgraf, R., and Neumann, I.D. (2004). Front. Neuroendocrinol. *25*, 150–176.

Landgraf, R., Keßler, M., Bunck, M., Murgatroyd, C., Spengler, D., Zimbelmann, M., Nussbaumer, M., Czibere, L., Turck, C.W., Singewald, N., et al. (2007). Neurosci. Biobehav. Rev. *31*, 89–102.

Lee, H.C. (2005). J. Biol. Chem. *280*, 33693–33696.

Ludwig, M., Sabatier, N., Bull, P.M., Landgraf, R., Dayanithi, G., and Leng, G. (2004). Nature *418*, 85–89.

Neumann, I.D., Ludwig, M., Engelmann, M., Pittman, Q.J., and Landgraf, R. (1993). Neuroendocrinology *58*, 637–645.

Nishimori, K., Young, L.J., Guo, Q., Wang, Z., Insel, T.R., and Matzuk, M.M. (1996). Proc. Natl. Acad. Sci. USA *93*, 11699–11704.

Poulain, D., Oliet, S., and Theodosis, D. (2002). Vasopressin and Oxytocin: From Genes to Clinical Applications (London: Elsevier).

Theodosis, D.T., Schachner, M., and Neumann, I.D. (2004). Eur. J. Neurosci. *20*, 3270–3280.

TOR and Aging: Less Is More

Stefan M. Schieke[1] **and Toren Finkel**[1,*]
[1] Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: finkelt@nih.gov
DOI 10.1016/j.cmet.2007.03.005

Metabolism and mitochondrial activity are thought to be important determinants of life span. A new study in this issue of *Cell Metabolism* (Bonawitz et al., 2007) suggests that the TOR pathway controls mitochondrial respiration in yeast and that the harder mitochondria work, the longer yeast live.

In 1928, the noted but controversial biologist Raymond Pearl published a treatise entitled *The Rate of Living, Being an Account of Some Experimental Studies on the Biology of Life Duration*, in which he argued that metabolic rate was the key determinant of an organism's life span. The immediate impact and acceptance of Pearl's idea was muted, perhaps due to the author's own flamboyant past, which included advocating the consumption of significant quantities of alcohol as a way to prolong life. Nonetheless, in contrast to his other ignoble theories, Pearl's work on metabolism was not completely dismissed. Indeed, 30 years later, it would coalesce with the work of Denham Harman and his "free-radical theory of aging" to form a single notion, that aging represents the end result of metabolically induced oxidant-mediated damage.

The Pearl-Harman notion was that faster metabolism (increased oxygen consumption) leads to increased reactive oxygen species (ROS) formation and hence shorter life span. Surprisingly, three-quarters of a century after Pearl's initial treatise, the molecular basis for differences in metabolic rate within and between organisms, as well as the relationship between oxygen consumption and ROS formation, remains largely unknown. Now, a paper in this month's issue of *Cell Metabolism* begins to peel away the mystery surrounding some of these decades-old questions (Bonawitz et al., 2007).

The current work centers on the TOR pathway in yeast and its role in aging. Yeast aging is usually analyzed in one of two different assays. Replicative life span is defined as the number of times a mother yeast cell can give rise to a daughter bud, while chronological life span is the length of time that a nondividing yeast cell can remain viable in culture. In mammals, this distinction may be analogous to assessing aging in dividing versus postmitotic cells. *S. cerevisiae* has two TOR genes that are partially but not completely redundant. Yeast deleted in the *TOR2* gene are not viable, while deletion of *TOR1* increases replicative life span (Kaeberlein et al., 2005). In general, TOR represents a central signaling node that coordinates cell growth with the underlying cellular energy state. In the presence of nutrients, when the energy stores of a yeast cell are high, TOR coordinates increases in translation, transcription, and ribosomal biogenesis while inhibiting the self-consuming process of autophagy. Interestingly, diminished TOR signaling can also extend the life span of other organisms

such as flies and worms (Kapahi et al., 2004; Vellai et al., 2003). In mammals, although much of the mechanics of TOR signaling is largely conserved, it is presently unknown whether diminished mTOR activity correlates with an extension of life span.

The new study (Bonawitz et al., 2007) extends these past observations by demonstrating that deletion of *TOR1* also leads to extension of chronological life span. Surprisingly, and in direct contrast to what Raymond Pearl would have predicted, long-lived yeast deficient in *TOR1* have greater rather than reduced oxygen consumption. In the present study, however, these differences in longevity and oxygen consumption were completely dependent on the presence of extracellular glucose. In wild-type yeast, the presence of glucose triggers a number of metabolic changes, but for our discussion, the most important is a shift whereby ATP is generated less from mitochondrial activity and more from anaerobic fermentation (see Figure 1). A similar glucose-dependent shift in respiration does not occur in mammals. Nonetheless, in wild-type yeast strains, shifting from glycerol to glucose as a carbon source triggers a decrease in mitochondrial respiration. The new study demonstrates that this mitochondrial shutoff does not happen to the same degree in *TOR1*-deleted yeast. Indeed, direct assessment of translation of mitochondria-encoded subunits revealed that the *TOR1*-deleted strain continuously synthesizes high levels of mitochondrial components compared to the wild-type strain. Together, these results suggest that, in yeast, TOR signaling might directly regulate mitochondrial biogenesis.

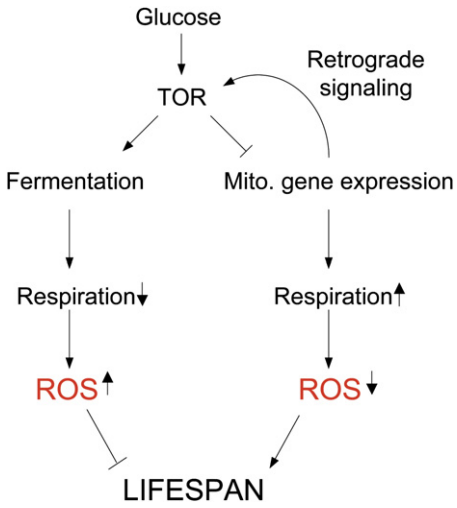

Figure 1. TOR Activity Negatively Regulates Life Span

Deletion of *TOR1* in yeast leads to life-span extension. In the manuscript by Bonawitz and colleagues (2007), this effect is only seen in the presence of glucose. Under these conditions, TOR1 sends a signal that inhibits mitochondrial activity, leading to a shift away from aerobic respiration and toward increased fermentation. This metabolic alteration is thought to lead to increased reactive oxygen species formation and a decrease in life span. In the absence of *TOR1*, this glucose-dependent decrease in respiration does not occur, and the continuation of high levels of mitochondrial activity promotes increased chronological life span. While TOR1 appears to regulate mitochondrial activity, the mitochondria can also influence TOR activity through a process known as retrograde signaling.

Bonawitz et al. (2007) provide a number of experiments suggesting that, in the *TOR1*-deleted strain, the relationship between increased mitochondrial activity and increased chronological life span may be causative and not merely correlative. For instance, deletion of *TOR1* does not lead to life-span increases in yeast strains deficient in mitochondrial respiration. Similarly, the authors demonstrate that other strains that are unable to undergo the glucose-induced shutoff of respiration are also long lived. This leads the authors to conclude that diminished TOR1 signaling extends life span by directly or indirectly regulating mitochondrial activity. This stands in contrast to other investigators who have argued that reducing TOR signaling increases longevity by mediating an increase in stress resistance (Powers et al., 2006). Interestingly, in mammalian cells, factors that stimulate increased mitochondrial numbers also appear to simultaneously orchestrate an increase in oxidant scavenging (St-Pierre et al., 2006), suggesting that, in some cases, increased stress resistance and augmented mitochondrial activity may be tightly coupled.

How does an increase in mitochondrial respiration lead to an increase in chronological life span? The mechanism proposed by Bonawitz et al. (2007) is a decrease in ROS formation. This supposition seems counterintuitive at first glance since ROS formation is a byproduct of respiration. Nonetheless, the formation of superoxide in the mitochondria requires two components to collide, molecular oxygen and a free electron. Busy mitochondria rapidly pass electrons down the electron transport chain and avidly consume oxygen, in doing so depleting the two components necessary for ROS formation. In this manner, it is proposed that an increase in respiration could lead to less—not more—ROS generation. This is also consistent with other data in yeast concerning the role of Sir2 and caloric restriction, where, again, there is evidence that the observed increase in replicative life span is mediated by increased mitochondrial activity (Lin et al., 2002).

It remains unclear how much of what has been learned in lower organisms will be directly transferable to mammals. For instance, we recently observed that in contrast to what is seen in the current study, in mammalian cells, mTOR activity positively correlates with mitochondrial activity (Schieke et al., 2006). A similar positive correlation in mammals between mTOR and mitochondrial biogenesis has also been observed by others (P. Puigserver, unpublished data). As Bonawitz et al. (2007) point out, this difference may be related to yeast's unusual propensity to favor anaerobic fermentation in the setting of extracellular glucose, a feat that mammalian cells, despite all of their sophistication, cannot duplicate. Nonetheless, all of these observations enlarge the sphere of influence of the TOR pathway to now include mitochondrial regulation. Previous studies have clearly shown that altering mitochondrial activity can, in what is known as retrograde signaling, feed back and regulate TOR activity (Liu and Butow, 2006). These new results suggest that a feed-forward pathway exists as well, wherein TOR activity regulates mitochondrial activity.

Many years after Raymond Pearl's "rate of living" theory was proposed, many fundamental questions remain unresolved. First among these is the simple question of whether more mitochondrial activity makes one live longer or not. Progress in this area has perhaps been stifled by the belief that aerobic metabolism is regulated solely by the availability of nutrients and reducing equivalents. Such notions are slowly giving way to a more nuanced view in which cellular signaling pathways intersect with the mitochondria, creating a two-way network of interactions between the consumer (the cell) and the supplier (the mitochondria) of energy. Undoubtedly, the answer to Pearl's 75-year-old question lies somewhere in this web of interactions.

ACKNOWLEDGMENTS

We are grateful to P. Puigserver for sharing unpublished observations and to I. Rovira for help with this manuscript.

REFERENCES

Bonawitz, N.D., Chatenay-Lapointe, M., Pan, Y., and Shadel, G.S. (2007). Cell Metab. *5*, this issue, 265–277.

Kaeberlein, M., Powers, R.W., 3rd, Steffen, K.K., Westman, E.A., Hu, D., Dang, N., Kerr, E.O., Kirkland, K.T., Fields, S., and Kennedy, B.K. (2005). Science *310*, 1193–1196.

Kapahi, P., Zid, B.M., Harper, T., Koslover, D., Sapin, V., and Benzer, S. (2004). Curr. Biol. *14*, 885–890.

Lin, S.J., Kaeberlein, M., Andalis, A.A., Sturtz, L.A., Defossez, P.A., Culotta, V.C., Fink, G.R., and Guarente, L. (2002). Nature *418*, 344–348.

Liu, Z., and Butow, R.A. (2006). Annu. Rev. Genet. *40*, 159–185.

Powers, R.W., 3rd, Kaeberlein, M., Caldwell, S.D., Kennedy, B.K., and Fields, S. (2006). Genes Dev. *20*, 174–184.

Schieke, S.M., Phillips, D., McCoy, J.P., Jr., Aponte, A.M., Shen, R.F., Balaban, R.S., and Finkel, T. (2006). J. Biol. Chem. *281*, 27643–27652.

St-Pierre, J., Drori, S., Uldry, M., Silvaggi, J.M., Rhee, J., Jager, S., Handschin, C., Zheng, K., Lin, J., Yang, W., et al. (2006). Cell *127*, 397–408.

Vellai, T., Takacs-Vellai, K., Zhang, Y., Kovacs, A.L., Orosz, L., and Muller, F. (2003). Nature *426*, 620.